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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/507,009	03/28/2005	Constantin G. Ioannides	UTSC:711US/10410987	7673

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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	
MAIL DATE	**DELIVERY MODE**
02/03/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/507,009	IOANNIDES ET AL.	
	Examiner	Art Unit	
	MARIANNE DIBRINO	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/10/09 & 10/26/09*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-8,10,12-32 and 44-55* is/are pending in the application.

4a) Of the above claim(s) *6,7,10,12,13,16-19,25,30,32,44,45,48-50,52-55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,5,8,14,15,20-24,26-29,31,46,47 and 51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/10/09 has been entered.

Applicant's amendment filed 10/26/09 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election without traverse of Group I and species of SEQ ID NO: 11 (KIFGSLA-iso-Phe-L), as well as "an increase in the antigen's ability to protect CTL's from activation induced cell death" as the species of "modulation of immunity" in Applicant's amendment and responses filed 7/20/07 and 7/28/08. The Examiner notes that SEQ ID NO: 11 has the unnatural amino acid residue iso-Phe at position 8 (P8). Iso-Phe differs from Phe in that iso-Phe lacks the CH_2 group between the phenol ring and the peptide bond.

Claims 8, 14, 15 and 28 read on the elected species.

Applicant is reminded that upon consideration of the prior art, examination had been extended to the species recited in instant claims 4, 5, 20-23, 26, 27, 29 and 31. Also, upon consideration of the art, claims 24 and 51 had also being included in examination.

Claims 4, 5, 8, 14, 15, 20-24, 26-29, 31 and newly added claims 46, 47 and 51 are presently being examined.

3. Applicant is reminded that the drawings are objected to because they contain handwritten text. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the Applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Applicant states in the amendment filed 10/26/09 that "Applicant's concurrently file herewith corrected drawing sheets in compliance with 37 C.F.R. 1.121(d)." However, the EFS Acknowledgement Receipt in response to the amendment filed 10/26/09 does not indicate that the corrected drawing sheets were filed.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 27 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The amendatory material not supported by the disclosure as originally filed is as follows: 'modulation of immunogenicity that comprises an increase in the antigens ability to activate low-avidity CTLs' (recited in claim 27) and 'the first substitute amino acid shortens the side chain as compared to the first amino acid' (recited in base claim 8).

The specification discloses at [0036] of the US 10050169934 A1 publication of the instant specification that low avidity CTL against tumor or pathogen-derived peptide antigens uses MHC binding peptides that have a CH2 side chain that is extended.

6. Claim 27 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not disclose how to make and/or use the instant invention, a method for preparing a peptide antigen analog with modulated immunogenicity, wherein said modulated immunogenicity comprises an increase in the antigens ability to activate low-avidity CTLs, and wherein the method comprises substituting at least a first amino acid residue located in a CTL epitope with a first substitute amino acid residue that is a non-natural amino acid residue selected from those recited in base claim 8, and wherein the first substitute amino acid residue shortens the side chain as compared to the first amino acid residue. The specification has not enabled the breadth of the claimed invention because the claim encompasses making a peptide analog that modulates immunogenicity in the opposite way by activating high-avidity CTLs rather than activating low-avidity CTLs. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed method can be used.

The specification discloses at [0036] of the US 10050169934 A1 publication of the instant specification that low avidity CTL against tumor or pathogen-derived peptide antigens uses MHC binding peptides that have a CH2 side chain that is extended.

Evidentiary reference Murray *et al* (Proc. Ann. Meeting of the Amer. Assoc. for Canc. Res. 7/03, 44: 765-66) teach that an E75 K53 variant (*i.e.,* Phe at TCR contact residue position 8 in the peptide changed to IsoPhe which shortens the side chain) was more effective in inducing high affinity CTLs. Thus, the evidentiary reference teaches that the opposite effect is obtained when the side chain is shortened.

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 4, 5, 8, 14, 15, 20-24, 26-29, 31, 46, 47 and 51 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: determining if the prepared peptide actually has modulated immunogenicity (commensurate with the preamble of the claims "A method for preparing a peptide antigen with modulated immunogenicity") and the steps leading up to the "substituting at least a first amino acid" residue with one of the recited non-natural amino acid residues (for example, determining the position(s) that are to be substituted).

The specification at the Examples sections discloses, for instance, that the E75 tumor associated peptide was modeled in the HLA-A2 class I MHC peptide binding groove, the position(s) in the peptide to be substituted was/were determined, certain peptide analogs were created with single amino acid substitutions (non-natural residues) at certain positions in the peptide in order to add one, two or three CH2 groups or to remove one CH2 group, the peptide analogs were evaluated for ability to induce different cytokines such as IFN-γ or IL-2, CTL tested for cross-reactivity against the wild-type peptide. The results disclosed in the specification indicate that different analogs behaved differently with regard to cytokine induction, cross-reactivity, peptide-induced CTL lytic activity, and that yields of high affinity CTL were influenced (higher yields) by the degree of attenuation of TCR signaling using less CH2-extended analogs. Claims 26-29 are included in this rejection because the recitation of "wherein modulation of immunogenicity comprises…" is not a method step, but is rather a property of the peptide analog that is produced by the method.

9. Claim 27 recites the limitation “wherein modulation of immunogenicity comprises an increase in the antigen's ability to activate low-avidity CTLs" at lines 1-3. This limitation lacks antecedent basis in claim 8, *i.e.,* base claim 8 recites "wherein the first substitute amino acid shortens the side chain as compared to the first amino acid." The specification discloses at [0036] of the US 10050169934 A1 publication of the instant specification that low avidity CTL against tumor or pathogen-derived peptide antigens uses MHC binding peptides that have a CH2 side chain that is extended.

10. Applicant’s amendment filed 10/26/09 has overcome the prior rejection of record of claims 3-5, 14, 23, 27-29, 31 and 46 under 35 U.S.C. 102(b) as being anticipated by Parker *et al* (J. Immunol. 1992, 149(6): 1896-1904, of record) as evidenced by an admission in the US 20050169934 A1 publication of the instant specification at [0036].

11. Applicant’s amendment filed 10/26/09 has overcome the prior rejection of record of claims 3-5, 14, 15, 24, 27-29 and 51 under 35 U.S.C. 102(b) as being anticipated by Krebs *et al* (J. Peptide Science, 1998, 4: 378-388) as evidenced by an admission in the US 20050169934 A1 publication of the instant specification at [0036].

12. Applicant’s amendment filed 10/26/09 has overcome the prior rejection of record of claims 3-5, 14, 15, 24, 27-29, 31 and 51 under 35 U.S.C. 102(b) as being anticipated by Rognan *et al* (PNAS USA 1995, 92: 753-757) as evidenced by an admission in the US 20050169934 A1 publication of the instant specification at [0036].

13. Applicant’s amendment filed 10/26/09 has overcome the prior rejection of record of claims 3-5, 14, 23, 20-22, 27-29, 31 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Parker *et al* (J. Immunol. 1992, 149(6): 1896-1904, of record) in view of Anderson *et al* (Cancer. Immunol. Immunother. 1999, 48: 401-410) as evidenced by an admission in the US 20050169934 A1 publication of the instant specification at [0036].

14. Claims 26-29, 31, 46 and 51 are objected to because of the following informality: “antigen’s” should be “antigens”.

Appropriate correction is required.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ram Shukla, can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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